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**13. ABSTRACT** *(Maximum 200 words)*

The objective of this study was to examine the effect of physical training in adolescent males and females on the interrelationship of the hypothalamic-pituitary-gonadal axis, bone mineral density, and incidence of stress fractures. Participants consisted of male and female Cadets enrolled at the U.S. Military Academy, West Point, NY. Both male and female Cadets had reduced plasma gonadal steroid levels during an intense period of physical training over the first six months of enrollment at the Academy. Female Cadets had a reduction in BMD with six months. Gains in bone mineral density were not noted until the second year in both males and females. In female Cadets who had persistently low estradiol levels, BMD did not increase over the study. In males with persistently low testosterone concentrations, BMD did not increase and was decreased compared to other subjects. The incidence of stress fractures was 6 percent and did not appear related to hypogonadism or low BMD. Initiation of rigorous physical training results in a period of hypogonadism and absence of BMD gain in both male and female adolescents. Persistence of hypogonadism is associated with attenuated BMD gain in both females and males. The initial incidence of stress fractures is similar in males and females and does not appear related to gonadal hormone levels or BMD. The undertaking by adolescents of rigorous physical training, which reduces gonadal steroid levels and BMD gain, does not appear to result in a significant incidence of stress fractures irrespective of gender.

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Charles E. Wade, Ph.D. July 1997

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## Abstract

**Objective.-** To examine the effect of physical training in adolescent males and females on the interrelationship of the hypothalamic-pituitary-gonadal axis, bone mineral density (BMD), and incidence of stress fractures.

**Design.-** Longitudinal study design with evaluation for 42 months.

**Setting.-** United States Military Academy, West Point, New York.

**Participants.-** Male (n=94) and female (n=84) Cadets enrolled at the Academy until graduation. Participants maintained a high level of physical fitness by taking part in rigorous training programs.

**Main Outcome Measures.-** Biannual measurements of plasma hormone levels and lumbar BMD, and the determination of the incidence of stress fractures from medical records and subject reporting.

**Results.-** Both male and female Cadets had reduced plasma gonadal steroid levels during an intense period of physical training over the first six months of enrollment at the Academy. Female Cadets had a reduction in BMD within six months. Gains in bone mineral density were not noted until the second year in both males and females. In female Cadets who had persistently low estradiol levels, BMD did not increase over the study. In males with persistently low testosterone concentrations, BMD did not increase and was decreased compared to other subjects. The incidence of stress fractures was 6% and did not appear related to hypogonadism or low BMD.

**Conclusions.-** Initiation of rigorous physical training results in a period of hypogonadism and absence of BMD gain in both male and female adolescents. Persistence of hypogonadism is associated with attenuated BMD gain in both females and males. The initial incidence of stress fractures is similar in males and females and does not appear related to gonadal hormone levels or BMD. The undertaking by adolescents

of rigorous physical training, which reduces gonadal steroid levels and BMD gain, does not appear to result in a significant incidence of stress fractures irrespective of gender.

Exercise by adolescents is advocated to increase bone mineral content and subsequently prevent osteoporosis in later life. [1-6] Exercise increases skeletal stress by weight bearing and muscle contraction, stimulating bone formation. [1,7-11] Exercise may also lead to "overuse injuries": those occurring at the onset of training in individuals not adequately conditioned, and those occurring in trained individuals due to overuse. [12-15] Stress fractures/overuse injuries associated with exercise are often disabling. Risk factors for exercise-related injuries and the long-term implications of these injuries are unknown. Further, the rate and manner of bone formation may not be the same in adolescents as in adults, putting adolescents at higher risk for injury. [16] Identification of adolescents at risk for stress fracture and modification of training programs for at-risk individuals could greatly reduce the incidence of these injuries. [15,17]

In poorly conditioned individuals, incidence of stress/overuse injuries is high upon initiation of training. [13,14,18-21] These individuals are usually injured within weeks of initiating training, with the incidence higher in women than in men. [13,18,20,22-24] Additional factors associated with onset-of-training injuries are race, [18,24] increasing age, [24] and excessive body weight. [13,22]

In trained subjects, stress fractures/overuse injuries are usually associated with intensive exercise over a period of time. [13,25] In male subjects, the incidence of stress fractures has been related to a decrease in bone density. [26] Incidence of injuries in female runners is associated with menstrual abnormalities, decreased estradiol levels, and diminished bone density. [12,25,27-29] The relationship of intense physical training and hypogonadism is complicated and not limited to females. Hypogonadism and decreased spermatogenesis have also been noted in males undergoing intensive training. [30-33] Thus, individuals performing intensive physical training appear to have a high incidence of hypogonadism.

In females, the association between reproductive function and bone density is well established, with a reduction in bone density associated with athletic amenorrhea. [25,28,34] Further, after resumption of menses in previously amenorrheic athletes, bone density is increased. [34,35] In males, bone loss associated with hypogonadism related to intensive training has not been as extensively studied [30,36] although there appears to be a relationship between intensity of exercise, hypogonadism, and increase in bone loss. Excessive exercise accompanied by a period of reduced nutritional intake with concomitant weight loss may prevent adolescents from attaining peak bone mass, placing them at increased risk for osteopenia later in life.

A serious consequence of exercise-related reproductive changes, and the concurrent low bone density, is the development of stress fractures. Such fractures occurred in a high percentage of female runners with amenorrhea, but in normal eumenorrheic runners and controls there were no fractures. [25,37] While an increase in overuse injuries in women athletes with menstrual irregularities has been demonstrated, [25,27,28,38,39] similar data is limited for males with hypogonadism. [4,36,40]

The present longitudinal study of Cadets at the United States Military Academy offered an opportunity to assess the interrelationship of hypogonadism, decreased bone density, and stress fracture/overuse injuries in adolescents. The Cadets were of both genders and initially undertook the same physical training, allowing evaluation of acute responses to training in males and females. As Cadets are required to maintain a high level of physical fitness throughout their four-year tenure at the Academy, assessment of the effects of long-term training was also possible. The present study evaluates the effect of physical training in young males and females on the hypothalamic-pituitary-gonadal axis, bone density, and incidence of stress fractures.

## Methods

The protocol was reviewed and approved by the Institutional Review Boards at the United States Military Academy and Letterman Army Institute of Research. All female Cadets and an equal number of male Cadets (every eighth individual on an alphabetical list) were asked to participate in a briefing on the study. Following the briefing, individuals were asked to volunteer for the study. Each individual later met separately with an investigator. Informed consent forms were then obtained.

Medical history and measurements (see below) were obtained within six days of enrollment at the Academy, July 1989. Eight weeks later, after an exceptionally intense period of physical training (equivalent to US Army "Basic Training"), measurements were again obtained. Measurements were repeated five months later and in subsequent 5–7 month intervals until graduation.

A medical history with a focus on overuse injuries was obtained on each subject and cross-checked biannually with medical records. A menstrual history was obtained for each female. Individuals were classified as oligomenorrheic if intervals between menses were greater than 3 months, and amenorrheic if menses was absent during the previous six months. Reproductive history and the use of birth control pills were recorded. All information was cross-checked by one of the investigators meeting individually with the subject.

Height and weight were measured, and body fat was determined using a skinfold caliper technique. [41] Skinfold measurements were taken by the same investigator throughout the study. Two-mile run time was determined in the course of the semiannual physical fitness test. These times were taken as indices of aerobic fitness. [42]

Venous blood samples were taken in a non-fasted state at each period of the study. Plasma was separated by centrifugation and frozen for later analysis. Samples were measured for serum calcium and phosphorous using an automated clinical assay system (Roche Analytical Instruments, Cobas FARA model). Plasma hormones were measured by radioimmunoassay. For females, estradiol, progesterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), immunoreactive parathyroid hormone (iPTH), and osteocalcin concentrations were determined. Blood samples were not drawn at a specific time of the menstrual cycle as this was not logistically possible due to stringent class schedules. In male subjects, free and total testosterone, iPTH, and osteocalcin levels were measured.

Bone density of the lumbar (L1-L4) spine was measured every 5–7 months according to standardized procedures using dual energy x-ray absorptiometery (DEXA model DPX, Lunar Corp., Madison, WI). Prior to obtaining measurements, calibration was done with a phantom of known density.

Subjects had daily access to medical care and the orthopedics department. If a stress related injury (stress fracture) was suspected, an x-ray was taken. If the x-ray was negative and the injury was not alleviated following a prescribed period of limited activity, bone scintigraphy was performed. Stress fractures were defined as an injury confirmed by x-ray or bone scintigraphy.

Data analysis was performed using an analysis of variance model (ANOVA) with time as a repeated measure (SAS). [43] To optimize the likelihood function, a Newton-Raphson algorithm was used; observations taken on each subject were therefore included in estimating the parameters. The model was adjusted for any gender differences. If a

significant effect was found, then the Newman-Keuls test was used to determine which means differed. A chi-square and/or Fisher's Exact test was used to assess categorical data. A significance level of $\alpha$=0.05 was used for all statistical tests.

## Results

Of 144 female Cadets at the Academy, 133 volunteered for the study. Of 150 male Cadets solicited, 136 males volunteered. Over the course of the study, a number of subjects were lost to follow-up (Table 1) because of withdrawal from the study or the Academy. Withdrawal from the study was defined as no data obtained after 24 months although the subject graduated. The final study population comprised 84 female and 94 male subjects.

[Table 1 here]

Height and weight of males was consistently ($p<0.001$) greater than that of females (Table 2). During the study, there was a slight, but significant ($p<0.001$), increase in height in both males and females, 0.6 cm and 0.8 cm, respectively. Females experienced increased body weight over the first six months, with no change thereafter. Males increased weight over the first six months proportionally to females, and had a progressive average increase of over 6.3 kg (8.6%) in the next three years. Both males and females reduced percent body fat in the first two months of training in the absence of a change in body weight. Females maintained this lower percent body fat. Percent body fat of males increased over the course of the study with an 18% increase observed. Two-mile run times, indices of aerobic fitness, were faster in the males (Table 2). The run times of males did not change, while the times of females decreased in the first year with no change over the subsequent three years.

[Table 2 here]

Bone mineral density (BMD) was lower in females throughout the study (Fig. 1). BMD changes over time were dependent on gender. Females had a significant ($p=0.015$) reduction in BMD over the first six months. BMD returned to baseline within a year, was maintained until the second year, and then increased at a rate of 0.018 $g/cm^2$/year. In males, there was no change ($p=0.061$) over the first six months with a progressive increase of 0.022 $g/cm^2$/year noted over the subsequent three years. Changes in BMD were due to changes in bone mineral content (BMC) as cross sectional area was not altered over time ($p=0.785$).

[Figure 1 here]

Plasma concentrations of calcium and phosphate tended to be greater in males compared to females (Table 3). Calcium levels rose over the first six months in both groups from initial values with no change thereafter. Phosphate concentrations showed a similar trend. Plasma iPTH concentrations were not altered in the males, while females had an increase at month 30. Males consistently had higher osteocalcin values ($p<0.0001$) than females. In both groups there was an increase in levels ($p<0.0001$) after 18 months.

[Table 3 here]

Plasma levels of estradiol and progesterone in females and testosterone (total and free) in males were low during the first year of the study (Fig. 2). These reductions in gonadal steroids coincided with the period when the intensity of physical exercise and stress are greatest for the Cadets. Plasma estradiol concentrations in females were reduced in the first two months of the study compared to subsequent measurements. Plasma concentrations of LH had similar changes, while no difference was noted in FSH (Table 3). A pattern similar to that of estradiol in females was noted for total testosterone and

free testosterone in males: values over the first two months were reduced compared to values in subsequent months.

[Figure 2 here]

There were 11 confirmed incidences of stress fractures in 10 (5.6%) subjects: two males and eight females. The incidence rate in males was 2.1% with both stress fractures occurring in the first seven months of the study. The rate in the females was 9.5% with 3 occurring in the first year of the study. While the incidence of stress fracture at the onset of training was not different between males and females, the overall incidence was greater in females ($p= 0.035$). Stress fractures in the subject experiencing two were separated by over a year. Body weights, percent fat, and two-mile run times of Cadets with stress fractures were within one standard deviation of the population means. Bone densities of subjects at the time of injury were compared to that of the population. In the male subjects, one had a level (1.31 $g/cm^{2)}$ well within the population range, while the other had the lowest BMD in the population (1.05 $g/cm^{2)}$. Neither of these individuals had additional incidence. For the females, the mean BMD at the time of injury was $1.26\pm0.032$ $g/cm^2$, similar to that of all females. In the subject who had a repeated injury, mean BMD was 1.28 $g/cm^2$, well within the population range of the present study.

## Female Subjects

*Birth Control Pills:* Of the 84 female subjects, 52 (62%) used birth control pills sometime during the study. The duration of use ranged from 6 to 42 months, with an average of $18\pm1.4$ months. In subjects who took birth control pills, estradiol levels were lower ($p=0.028$) with no difference noted in progesterone concentrations. There was no difference in BMD in subjects who had taken birth control pills compared to those who

had not. Of the eight females who had stress fractures, four had taken birth control pills at some time during the study and four had not.

*Menstrual Irregularities:* Only eight (9.5%) female subjects reported menstrual irregularities. Two of these were amenorrheic (of these, one had had a hysterectomy and was receiving oral estrogen replacement) for the duration of the study. The other six were oligomenorrheic for 3 to 12 months. Those subjects with menstrual irregularities had lower ($p=0.014$) percent body fat throughout the study compared to subjects who were eumenorrheic. There were no differences in body weight. There was no difference in BMD from subjects who were eumenorrheic and those who were oligomenorrheic. None of the subjects reporting menstrual irregularities was diagnosed with a stress fracture.

*Plasma Estradiol Level <25 pg/ml:* There were 11 subjects (13%) with a mean estradiol level less than 25 pg/ml over the period of the study. The mean estradiol concentration in these subjects was 17.6±1.4 pg/ml compared to 64.7±2.8 pg/ml for the rest of the population. Plasma progesterone levels were also decreased in these subjects. There was no significant difference in BMD in subjects who had low estradiol levels compared to the other subjects (Fig. 3a). Subjects with low plasma estradiol levels did not show a significant gain in BMD over the course of the study. The subject who had two stress fractures had a mean estradiol level of less than 25 pg/ml. There were no other occurrences of stress fractures in this group of subjects.

[Figure 3 here]

## Male Subjects

*Plasma Free Testosterone <18 pg/ml and Total Testosterone <350 ng/ml :* Of the male subjects, 12 (13%) had a mean free testosterone level <18 pg/ml and total testosterone of

<350 ng/ml over the 42 months of the study. The mean plasma free testosterone level in these subjects was 15±0.07 pg/ml compared to 21±0.4 pg/ml for the other subjects. Total testosterone was also reduced in these subjects with average cumulative mean value of 297±14.1 ng/ml in contrast to 466±9.9 n9/ml for the rest of the study population. There was a significant overall lower (p=0.025) in BMD in males with low free testosterone levels (Fig 3b). This difference persisted over the course of the study. Of the two males who had stress fractures, one met the criteria of having low free testosterone levels.

## Discussion

Upon enrollment at the U.S. Military Academy, young males and females are exposed to an intense physical and academic curriculum. This type of training has been reported to result in a high incidence of stress fractures, especially in females. [13,18,20,22-24] In the present study, the incidence rate of stress fractures following the initial period of training was low, <4%, in both females and males compared to earlier reports. [20] This low incidence may be due to the injury criteria used in the present study (positive x-ray or bone scintigraph), the ready availability of orthopedic personnel to the Cadets throughout their training, or increased awareness of training personnel of the potential for injury (a study effect may have occurred such as changing to running shoes from boots at the first signs of discomfort). Over the course of the study, the incidence of stress fractures tended to be higher in females, 10%, compared to 2% in the males. This gender difference in the incidence of stress fractures has been suggested to be due to differences in body composition, physical conditioning, menstrual dysfunction induced by training, bone density, or hypogonadism. [12,16,44,45]

Progressively over the course of the study, males gained both weight and percent body fat. Females also gained weight in the first year but subsequently maintained their percent body fat. After the first year, females maintained both body weight and percent fat. It has been suggested that body mass positively influences BMD. [46,47] In the females in the present study, an increase in BMD occurred in the absence of changes in body weight. The weight gain in males, however, could have imparted some influence on the observed gain in BMD. As to the possibility of body mass contributing to skeletal injuries, subjects sustaining injuries in the present study were well within body weight and percent fat norms for their ages [48,49] and there was no relationship of injury to body weight or composition.

In the present study, based on two-mile run times, physical conditioning appeared to improve in females. However, inherent differences in physical conditioning could in part account for the greater incidence of stress fractures in the females who were required to participate in all training and challenged to expend the same relative effort as the men. [11,50,51]

In females who reported menstrual dysfunction, there was a reduced percent body fat. The low body fat has been related to the occurrence of menstrual irregularities (i.e. oligomenorrhea), [52] but has not been associated with exercise-induced amenorrhea. [38] Additionally, athletes who have menstrual dysfunction have a decreased bone density and a greater incidence of stress fractures. [12,25,27,28] In the present study, 9.5% of the females reported periods of menstrual irregularities. This rate is significantly less than reported previously in women athletes and at the Academy. [1,20,21,53] There was no difference noted in bone mineral density or incidence of stress fractures in subjects with menstrual irregularities. Menstrual irregularities did not appear to be related to the physical training in the present study or to the incidence of stress fractures.

For subjects who had stress fractures, BMD was similar to that of the overall population. Low BMD was not a consistent finding in those subjects who were injured. This is in contrast to earlier work that suggested that low BMD was associated with increased stress fractures in female athletes. [12,25,26] The increased overall incidence of stress fractures and the occurrence of injuries beyond the first two months in females compared to males may be related to lower BMD over the course of the study.

Though hypogonadism appears related to changes in BMD (see below), it does not appear related to the occurrence of stress fractures. In the 10 subjects who had stress

fractures, the percentage with hypogonadism, 20%, was similar to that in the entire study population, 13%. In subjects with hypogonadism, the incidence of fractures, 8%, was similar to that of the overall population, 6%.

Both males and females showed an effect of initial intense training on BMD that may be related to hypogonadism. Over the first 6 months, females had a decrease and males no change in BMD. Usually during this age period, there is a gain in BMD. [2,3,54-56] Further, Marcus et al.[1] found eight months of moderate exercise by college age females increased BMD. In contrast, the present study showed a loss in BMD gain with the onset of training; the loss persisted for over a year (Fig 1). Subsequently, there was an increase in BMD with the rate per year being similar to that previously reported for young males and exceeding that reported for equivalently aged females. [3,54] The initial slow rate of gain in BMD was likely associated with a period of hypogonadism: low estradiol or testosterone. The association of hypogonadism with BMD is variable but suggests that a decrease in hormone levels leads to a reduction in bone formation. [9,57,58] The levels of these hormones in the initial period of the study were well below normal (Fig. 2). Further, during this period, osteocalcin levels were reduced though similar to levels reported previously for equivalent age groups [59,60] (Table 3). Osteocalcin levels are representative of osteoblast activity and are thus associated with changes in bone formation and disturbances in bone turnover. In the present study, the higher osteocalcin levels late in the study would be indicative of an increase in bone formation possibly contributing to the increase in BMD. Previous work has shown osteocalcin levels to be related to gonadal steroid concentrations in youngsters. [58,61] In the present study, osteocalcin concentration tended to follow a pattern similar to that of the changes in estradiol and testosterone, increasing over the initial year of the study. Plasma levels of gonadal steroids have been shown to be reduced in response to an increase in training. [30-32] They are also decreased with the onset of heavy academic requirements and lack of sleep.

[62-64] Thus, in the present study, the reduction of gonadal steroids may be related to the environment. The decrease in gonadal steroids could contribute to the reduction in bone formation and subsequently BMD over the first year of the study. This idea is supported by the persistently reduced BMD in male subjects with low free testosterone levels. The lower rate of gain in BMD in females with low estradiol levels adds further credence.

While the incidence of stress fractures tended to be greater in females than males, it was less than previously reported for this population. [20,21] The incidence of stress fractures upon initiation of training was not different between males and females. The occurrence of stress fractures appeared unrelated to body weight or composition, level of conditioning, menstrual dysfunction, level of bone density, or hypogonadism. Upon enrollment at the Academy and undertaking of an intense physical training program, both males and females showed similar responses: low levels of gonadal steroids, no gain in bone mineral density, and decreases in body fat. Over the subsequent 42 months of the study, there was a normalization of gonadal steroid levels and an increase in bone mineral density in both male and female Cadets. In summary, adolescents initially undertaking rigorous physical training reduce gonadal steroid levels and BMD gain, which do not appear to result in a significant incidence of stress fractures, irrespective of gender. As exercise continues, the overall incidence of stress fractures is greater in females, possibly related to their lower BMD. Still unknown are the long-term effects of intensive exercise as an adolescent on the attainment of peak bone mass as an adult.

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Table 1. Distribution of the study population.

| | FEMALES | MALES |
|---|---|---|
| Volunteered | 133 | 136 |
| Withdrew from study | 7 (5%) | 14 (10%) |
| Withdrew from Academy | 42 (31%) | 28 (21%) |
| Available for study | 84 (63%) | 94 (69%) |

Table 2. Subject characteristics and exercise performance.

| NUMBER OF MONTHS | 0 | 1 | 6 | 13 | 18 | 25 | 30 | 37 | 42 |
|---|---|---|---|---|---|---|---|---|---|
| DATE | JUL-89 | AUG-89 | JAN-90 | AUG-90 | JAN-91 | AUG-91 | JAN-92 | AUG-92 | JAN-93 |
| Height (cm) | | | | | | | | | |
| Female | 167±0.7 | 167±0.7 | 168±0.7 | 167±0.7 | 167±0.7 | 167±0.7 | 167±0.7 | 168±0.7 | 168±0.7 |
| Male | 179±0.7 | 179±0.7 | 179±0.7 | 180±0.7 | 179±0.7 | 180±0.7 | 180±0.7 | 180±0.7 | 180±0.7 |
| Body Weight (kg) | | | | | | | | | |
| Female | 60±0.9 | 60±0.9 | 63±0.9 | 63±0.9 | 62±0.9 | 62±0.9 | 62±0.9 | 62±0.9 | 63±0.9 |
| Male | 73±0.8 | 74±0.8 | 75±0.8 | 76±0.8 | 77±0.8 | 77±0.8 | 78±0.8 | 79±0.8 | 80±0.9 |
| Body Fat (%) | | | | | | | | | |
| Female | 26.1±0.41 | 24.8±0.41 | 25.1±0.40 | 25.7±0.40 | 26.1±0.40 | 25.4±0.41 | 25.0±0.41 | 24.8±0.41 | 25.2±0.43 |
| Male | 14.4±0.38 | 13.6±0.38 | 14.4±0.38 | 14.5±0.38 | 15.5±0.38 | 15.2±0.38 | 15.4±0.39 | 16.1±0.40 | 17.1±0.42 |
| Two-Mile Run (min) | | | | | | | | | |
| Female | - | 16.5±0.17 | 15.0±0.17 | 15.2±0.17 | 15.3±0.17 | 15.3±0.17 | 15.1±0.17 | 15.1±0.17 | 15.3±0.17 |
| Male | - | 13.3±0.16 | 13.1±0.16 | 13.2±0.16 | 13.2±0.16 | 13.1±0.16 | 13.1±0.16 | 13.0±0.16 | 13.3±0.16 |

Table 3. Plasma concentrations.

| NUMBER OF MONTHS | 0 | 1 | 6 | 13 | 18 | 25 | 30 | 37 | 42 |
|---|---|---|---|---|---|---|---|---|---|
| DATE | JUL-89 | AUG-89 | JAN-90 | AUG-90 | JAN-91 | AUG-91 | JAN-92 | AUG-92 | JAN-93 |
| Calcium (mg/dl) | | | | | | | | | |
| Female | 9.3±0.07 | 9.7±0.07 | 9.9±0.07 | 9.7±0.07 | 9.5±0.07 | 9.8±0.07 | 9.8±0.07 | 9.2±0.07 | 9.9±0.07 |
| Male | 9.6±0.06 | 9.9±0.06 | 9.9±0.07 | 10.0±0.07 | 10.0±0.07 | 10.0±0.07 | 10.3±0.06 | 9.8±0.07 | 9.9±0.07 |
| Phosphate (mg/dl) | | | | | | | | | |
| Female | 3.01±0.07 | 3.11±0.07 | 3.66±0.07 | 3.47±0.07 | 3.99±0.07 | 3.77±0.07 | 3.77±0.06 | 3.59±0.07 | 3.79±0.07 |
| Male | 3.40±0.06 | 3.51±0.06 | 3.50±0.07 | 3.52±0.06 | 3.89±0.07 | 3.89±0.07 | 3.96±0.06 | 3.61±0.07 | 3.90±0.07 |
| Parathyroid (pg/ml) | | | | | | | | | |
| Female | 27±2.6 | 22±2.6 | - | 24±2.6 | - | 29±2.7 | 40±2.6 | - | 34±2.7 |
| Male | 32±2.4 | 33±2.4 | - | 33±2.4 | - | 29±2.6 | 30±2.4 | - | 34±2.7 |
| Osteocalcin (ng/ml) | | | | | | | | | |
| Female | 2.4±0.22 | 2.5±0.22 | 2.1±0.22 | - | 4.3±0.22 | - | 5.1±0.22 | - | 3.4±0.23 |
| Male | 4.6±0.21 | 4.2±0.21 | 5.0±0.21 | - | 6.7±0.22 | - | 7.1±0.21 | - | 4.7±0.23 |
| Follicle Stimulating Hormone (mIU/ml) | | | | | | | | | |
| Female | 7.4±1.58 | 11.8±1.57 | 11.4±1.59 | 9.1±1.59 | - | 11.0±1.67 | - | 10.6±1.6 | - |
| Luetinizing Hormone (ng/dl) | | | | | | | | | |
| Female | 6.7±1.81 | 8.6±1.8 | 16.1±1.83 | 12.6±1.82 | - | 16.3±1.97 | - | 14.1±1.85 | - |

**Figure 1.** Comparison of bone mineral density in female and male Cadets over the four years of the study. Values are mean±SD.

**Figure 2.** Comparison of plasma estradiol and progesterone concentration levels (females) and plasma free and total testosterone concentration levels (males) over the four years of the study. Values are mean±SD.

**Figure 3.** Comparison of bone mineral density over the four years of the study for A: females with plasma estradiol concentration levels of $<$ or $\geq$ 25 pg/ml, and B: males with plasma testosterone levels of $\geq$ 18 pg/ml and total testosterone concentration $<$350 ng/ml compared to the rest of the male subjects. Values are mean±SD.

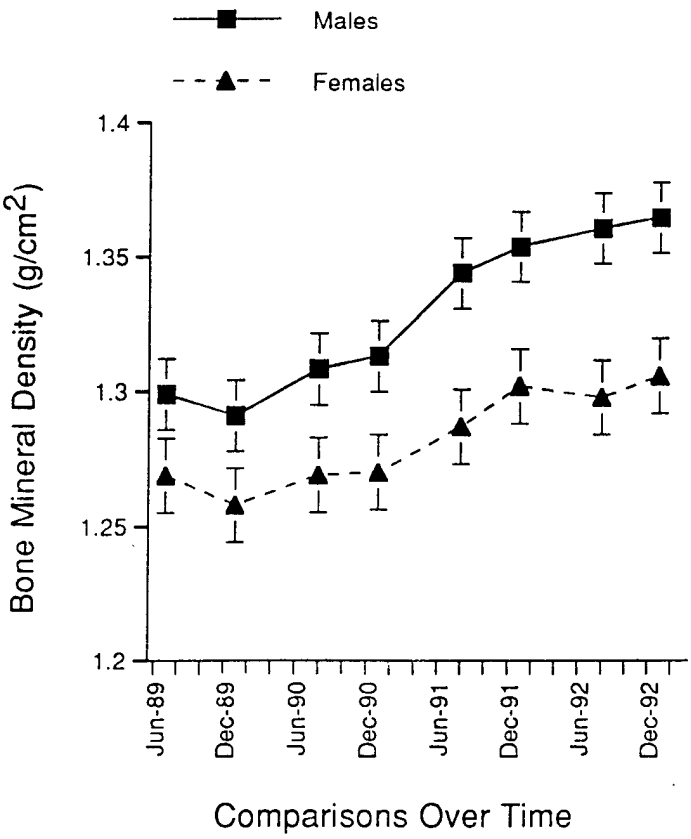
Males
Females
1.4
1.35
1.3
1.25
1.2
Bone Mineral Density (g/cm2)
Jun-89
Dec-89
Jun-90
Dec-90
Jun-91
Dec-91
Jun-92
Dec-92
Comparisons Over Time

Figure 1.

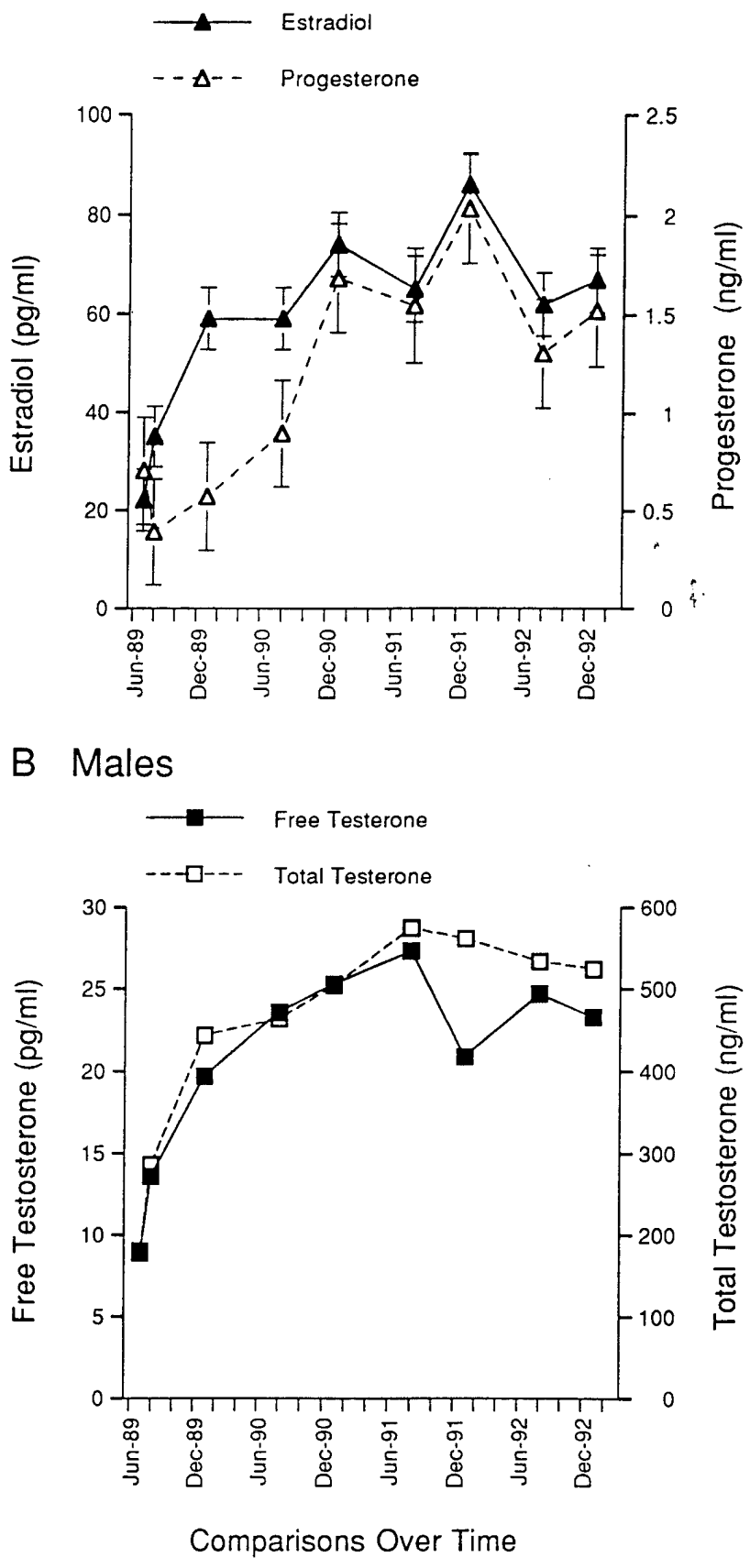
A Females
Estradiol
Progesterone
Estradiol (pg/ml)
Progesterone (ng/ml)
100
80
60
40
20
0
2.5
2
1.5
1
0.5
0
Jun-89
Dec-89
Jun-90
Dec-90
Jun-91
Dec-91
Jun-92
Dec-92
B Males
Free Testerone
Total Testerone
Free Testosterone (pg/ml)
Total Testosterone (ng/ml)
30
25
20
15
10
5
0
600
500
400
300
200
100
0
Jun-89
Dec-89
Jun-90
Dec-90
Jun-91
Dec-91
Jun-92
Dec-92
Comparisons Over Time

Figure 2.

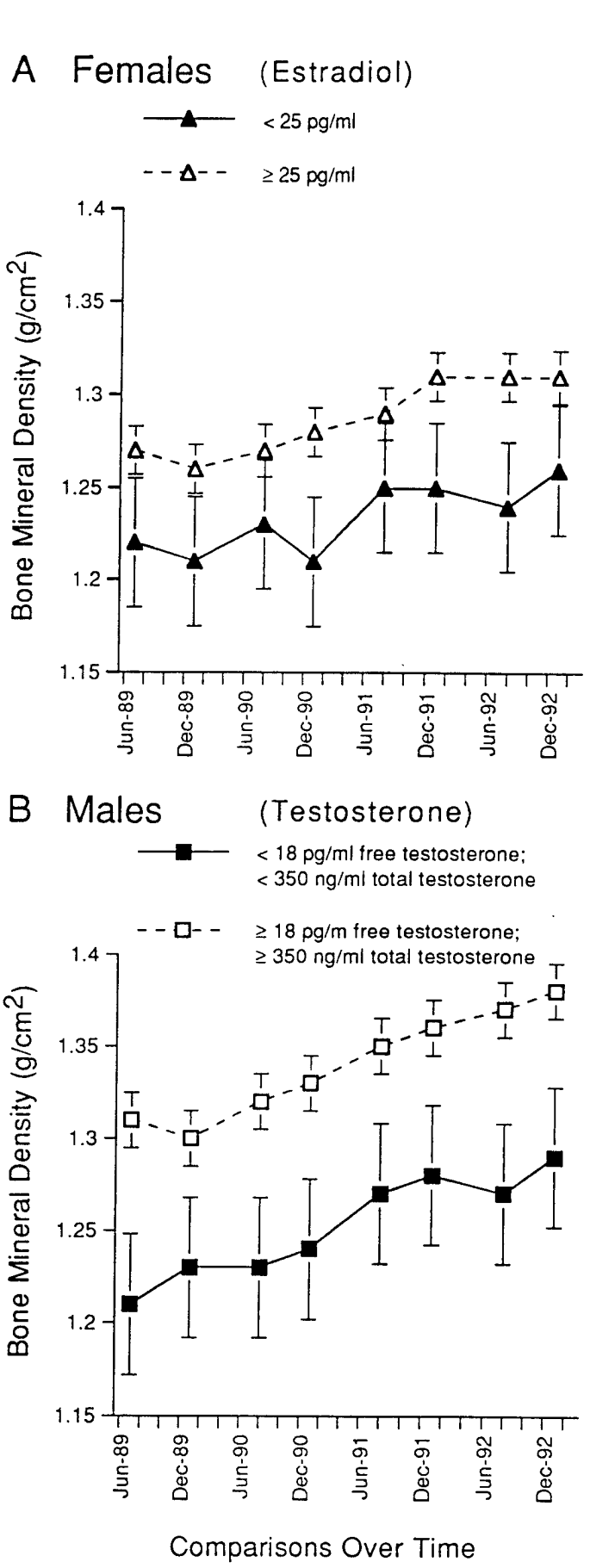
A Females (Estradiol)
< 25 pg/ml
≥ 25 pg/ml
Bone Mineral Density (g/cm2)
1.4
1.35
1.3
1.25
1.2
1.15
Jun-89
Dec-89
Jun-90
Dec-90
Jun-91
Dec-91
Jun-92
Dec-92
B Males (Testosterone)
< 18 pg/ml free testosterone;
< 350 ng/ml total testosterone
≥ 18 pg/m free testosterone;
≥ 350 ng/ml total testosterone
Bone Mineral Density (g/cm2)
1.4
1.35
1.3
1.25
1.2
1.15
Jun-89
Dec-89
Jun-90
Dec-90
Jun-91
Dec-91
Jun-92
Dec-92
Comparisons Over Time

Figure 3.